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**Datasheet for the decision
of 12 July 2018**

Case Number: T 2316/15 - 3.3.07

Application Number: 10012336.3

Publication Number: 2272507

IPC: A61K9/70, A61K31/485

Language of the proceedings: EN

Title of invention:

Transdermal formulation comprising an opioid analgesic and an aloe composition

Patent Proprietor:

Luye Pharma AG

Opponent:

LTS LOHMANN Therapie-Systeme AG

Headword:

Transdermal formulation/ LTS

Relevant legal provisions:

RPBA Art. 12(4), 13(1)

EPC Art. 56

Keyword:

Documents submitted with the statement of grounds of appeal -
admitted (yes)

Late-filed documents - admitted (no)

Inventive step - (no)



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Case Number: T 2316/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 July 2018

Appellant: LTS LOHMANN Therapie-Systeme AG
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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
8 October 2015 concerning maintenance of the
European Patent No. 2272507 in amended form.**

Composition of the Board:

Chairman J. Riolo
Members: A. Usuelli
Y. Podbielski

Summary of Facts and Submissions

- I. European patent No. 2 272 507 was opposed on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

The following documents were among those cited during the first-instance proceedings:

D6: US 2003/0064093

D7: WO 98/01167

D9: DE 19654468

- II. The appeal of the opponent lies against the decision of the opposition division according to which the subject-matter of the main request filed on 10 August 2015 (as auxiliary request 1) met the requirements of the EPC.

Claim 1 of this request read as follows:

"1. Transdermal patch comprising
- an opioid analgesic from the phenanthrene group or a pharmaceutically acceptable salt thereof as active ingredient,
- an aloe composition as transdermal penetration agent and
- a covering layer, a pressure sensitive adhesive and a release liner, wherein the adhesive consists of or comprises a rubber adhesive selected from a styrene-butadiene-styrene block copolymer and a styrene-butadiene block copolymer".

The opposition division held that the main request complied with the requirements of Articles 123(2) and 54 EPC and was sufficiently disclosed. It furthermore considered that the modification in Table 1 of the description (example 1) of the unit "g/(cm²*h)" into "µg/(cm²*h)" was a correction of an obvious error that complied with Rule 139 EPC.

As to inventive step, the opposition division held that the subject-matter of the main request differed from the disclosure of D9, selected as the closest prior art, in the presence of an aloe vera composition as transdermal penetration agent and in the composition of the adhesive. The data in table 1 of the patent demonstrated that the presence of aloe vera increased the transdermal flux of the active ingredient. This effect was not suggested in any of the prior art document. Hence, the subject-matter of claim 1 of the main request could not be derived in an obvious manner from this state of the art.

III. With the statement setting out the grounds of appeal filed on 18 February 2016 the appellant requested that the decision under appeal be set aside and the patent be revoked. It furthermore submitted the following documents:

D16: Health Foods Business, February 1994, 23-24

D17: CAS presents: "Common chemistry"

IV. The patent-proprietor (hereinafter: the respondent) replied to the appeal of the opponent by letter of 4 July 2016. It requested to dismiss the appeal (i.e. to maintain the patent on the basis of the request considered by the opposition division to comply with the EPC) and filed five auxiliary requests.

Claim 1 of auxiliary request 1 was identical to claim 1 of the main request.

Claim 1 of auxiliary request 2 differed from claim 1 of the main request in specifying that the opioid analgesic was buprenorphine.

Claim 1 of auxiliary request 3 differed from claim 1 of the main request in that the feature "wherein the adhesive consists of or comprises a rubber adhesive" was modified to read "wherein the adhesive consists of a rubber adhesive" (i.e. deletion of the option "or comprises").

Claim 1 of auxiliary request 4 was identical to claim 1 of auxiliary request 2.

Claim 1 of auxiliary request 5 was based on the combination of the amendments incorporated into claim 1 of auxiliary requests 2 and 3.

V. By letter of 6 April 2017 the appellant submitted the following documents:

D19: Erklärung of Dr Hille

D20: Kleben - Grundlagen, Technologie, Anwendungen, 2006, 191, 192.

VI. On 23 May 2018, the Board issued a communication pursuant to Article 15(1) RPBA. With regard to the requirement of inventive step it observed that the closest prior art D9 did not disclose any patch containing aloe vera and an adhesive as defined in claim 1. It commented that the obviousness of claim 1 of all the request was to be considered in the light of

the teaching of D9 in combination in particular with D6 and D16.

VII. Oral proceedings took place as scheduled on 12 July 2018.

VIII. The arguments of the appellant, as far as they are relevant to the decision, can be summarised as follows:

(a) Admittance of documents D16, D17, D19 and D20

Documents D16 and D17 were filed with the statement setting out the grounds of appeal. D16 provided information as to the properties of aloe vera. D17 related to the commercial product Durotak® 6173 used in example 1 of the patent. D19 and D20 were filed in support of the argument that a skilled person would have not been able to prepare an adhesive consisting of a SBS copolymer.

(b) Inventive step

Document D9 was the closest prior art for the assessment of inventive step. The patch of the main request differed from those disclosed in D9 mainly in the presence of aloe vera as transdermal penetration agent. As to the composition of the adhesive, D9 referred to copolymers of the same family of the copolymers of the main request. SBS and SB copolymers were in any case known from D7. The experiments disclosed in the patent were not suitable to demonstrate that aloe vera increased the transdermal penetration. Indeed there was no comparison with a patch that did not contain aloe vera and it was not clear whether the higher flux observed for the first patch was due to the amount of aloe vera or the amount

of active ingredient. Moreover, the experiment was not suitable to demonstrate a capillary uptake of the active ingredient which was an essential step in the transdermal absorption. The technical problem was therefore to be seen in the provision of an alternative transdermal patch. The use of aloe vera in compositions for transdermal patches was disclosed for instance in D6 and D16. Hence, on the basis of these prior art documents the skilled person would have arrived at the subject-matter of the main request without any inventive effort.

The same arguments applied to the subject-matter of the auxiliary requests.

IX. The arguments of the respondent, as far as they are relevant to the decision, can be summarised as follows:

(a) Admittance of documents D16, D17, D19 and D20

Documents D16 and D17 were not *prima facie* relevant. D19 and D20 were very late filed and represented the first pieces of evidence filed by the appellant in support of its argument that it was not possible to prepare adhesive consisting of SBS copolymers. None of these documents was to be admitted into the appeal proceedings.

(b) Inventive step

Example 1 of the patent was clear evidence that aloe vera had a positive effect on the transdermal absorption. Document D9, representing the closest prior art, did not provide this teaching. The same conclusion applied to D16. This document merely indicated that aloe vera enhanced the penetration of other substances

into the skin. However, it did not suggest that aloe vera also promoted the transdermal absorption. This teaching could neither be derived from document D6 which also described the use of aloe vera as skin penetration enhancer. Concerning the composition of the adhesive, document D9 referred to several suitable polymers however it did not describe any patch wherein the adhesive was based on the same SBS or SB copolymers specified in claim 1 of the main request. These specific copolymers offered the advantage of preventing the crystallisation of the active ingredient. This effect contributed to the transdermal penetration of the active ingredient. D9 was silent also in this regard.

The same arguments applied to the subject-matter of the auxiliary requests.

- X. The appellant requested that the decision under appeal be set aside and the patent be revoked.

- XI. The respondent requested that the appeal be dismissed or, as an auxiliary measure, that the patent be maintained on the basis of one of auxiliary requests 1-5, all filed with letter dated 4 July 2016. The respondent also requested not to admit documents D16, D17, D19 and D20 into the proceedings.

Reasons for the Decision

- 1. Admittance of documents D16, D17, D19 and D20
 - 1.1 Documents D16 and D17 have been filed by the appellant with the statement setting out the grounds of appeal.

These documents are part of the appeal proceedings unless it is concluded that they should have been presented during the first instance proceedings (Article 12(4) RPBA).

- 1.1.1 D16 describes some property of aloe vera and its use in transdermal compositions. It supports the appellant's position, already expressed during the first instance proceedings, that a skilled person would include aloe vera in a transdermal patch. Document D17 provides information as to the chemical composition of the polymer Durotak® 6173 used in example 1 of the patent. The composition of the Durotak products is discussed in the decision under appeal in relation to the requirement of sufficiency of disclosure.
- 1.1.2 Thus, both documents have been filed to reinforce lines of attack already taken before the opposition division. In the Board's view the filing of D16 and D17 was a legitimate response to the decision of the opposition division and there were no compelling reasons for the appellant to file documents D16 and D17 at an earlier stage. Hence, the Board decides to admit documents D16 and D17 into the opposition proceedings.
- 1.2 The appellant filed documents D19 and D20 during the appeal proceedings with letter dated 6 April 2017.
 - 1.2.1 D19 is an expert declaration containing experimental data. D20 is a document referred to in D19, published after the filing date of the patent-in-suit. Both documents should support the appellant's attack on sufficiency of disclosure based on the argument that the skilled person would not be able to prepare pressure sensitive adhesives consisting of SBS copolymers.

- 1.2.2 During the proceedings before the opposition division, the appellant did not file any document in support of this line of attack (see point 4.2 of the decision). Nor did it file any evidence with the statement setting out the grounds of appeal. Documents D19 and D20 are therefore the first documents that should corroborate the argument that a skilled person would not be able to perform the invention when the adhesive consists of SBS copolymers. Before the filing of these documents, the appellant based its objection on mere statements.
- 1.2.3 In the absence of a specific reason justifying the late-filing, the Board considers that the appellant should have filed documents D19 and D20 at an earlier stage of the proceedings. In view of this, and considering the advanced stage of the proceedings as well as the need for procedural economy, the Board decides not to admit documents D19 and D20 into the appeal proceedings (Article 13(1) RPBA).

Main Request

2. The appellant had contended that a correction made in the description during the examination proceedings, replacing the unit "g/(cm²*h)" with the unit "µg/(cm²*h)", did not comply with the requirements of Rule 139 EPC and that this amendment thus contravened Article 123(2) EPC. Whilst this point was discussed during the oral proceedings and considered by the Board, whether the correction complies or not with Rule 139 EPC has no impact on the inventive step objection that led to the revocation of the patent (see points 3 to 5 below). For the ease of reference, the corrected version of Table 1 of example 1 is referred to further below in this decision.

3. Inventive step

3.1 Closest prior art

3.1.1 The Board considers, in agreement with the decision under appeal, that document D9 is the closest prior art. This document describes patches that comprise a backing layer, an adhesive, a matrix containing the adhesive and a release liner (column 2, lines 21 to 26). The active ingredient can be for instance buprenorphin (column 4, line 20) and the adhesive can be made of styrene-butadiene-styrene-isoprene copolymers (column 3, lines 12 and 13). D9 furthermore indicates that the patch can contain a vegetable extract such as aloe vera (column 4, line 67).

D9 does not disclose any patch containing aloe vera and an adhesive defined as in claim 1 of the main request.

3.2 Technical problem

3.2.1 In the respondent's opinion, the results disclosed in example 1 of the patent demonstrate that the inclusion of aloe vera in the matrix of a buprenorphine matrix patch results in an increase of the transdermal absorption of the active ingredient.

3.2.2 In the experiment described in example 1, three patches containing different amounts of buprenorphine and aloe vera have been applied to female hairless mouse skin. Table 1 of example 1 reports for each patch the flux of the active ingredient.

3.2.3 The Board agrees with the respondent that this experiment is based on an *in vitro* model and as such it

cannot provide any data as to the buprenorphine concentration in the blood. However, paragraph [0004] of the description explains that the transdermal absorption involves a sequence of five steps the last one being the capillary uptake of the active ingredient. Thus, the experiment of example 1 is not suitable to make an assessment of the absorption of buprenorphine since there is no measurement of the drug concentration into the circulating blood.

- 3.2.4 Regardless of the considerations made in the previous paragraph, the Board is in any case of the view that the results of example 1 do not clearly demonstrate the presence of an effect associated with the inclusion of aloe vera in the matrix composition.

In this regard, it is observed that the respondent focused its analysis of Table 1 on the flux data relating to patches 2 and 3 which are $0,8 \mu\text{g}/\text{cm}^2\cdot\text{h}$ and $0,9 \mu\text{g}/\text{cm}^2\cdot\text{h}$, respectively. Patch 2 contains 5% buprenorphine and 20% aloe vera whereas patch 3 contains 10% buprenorphine and 10% aloe vera. In the respondent's view, the fact that the flux of patch 2 is very close to the one of patch 3, despite the fact of containing much less buprenorphine, is due to the fact that it contains a double amount of aloe vera. Hence, in the respondent's opinion it follows from a comparison of patches 2 and 3 that aloe vera increases the flux of buprenorphine.

- 3.2.5 On the other hand, as remarked by the appellant, the flux data relating to patch 1 suggests that also the concentration of buprenorphine affects the flux. Indeed, the flux of patch 1 is $2,3 \mu\text{g}/\text{cm}^2\cdot\text{h}$, i.e much higher than the fluxes of patches 2 and 3. Patch 1 contains the highest concentration of buprenorphine

among the three patches (15%) and the same amount of aloe vera as patch 2 (20%).

- 3.2.6 In the Board's view, the data of Table 1 indicate that the buprenorphine concentration and aloe vera concentration together influence the flux of active ingredient. It is however impossible to ascertain on the basis of Table 1 whether the addition of aloe vera alone is a factor that increases the flux of active ingredient and in that case to what extent. This is a relevant issue when assessing example 1 in the context of defining the technical problem over D9, since the buprenorphine concentration is not a distinguishing feature over D9.

To assess the effects of aloe vera on the flux of active ingredient it would have been necessary to compare two patches differing only in the amount of aloe vera. For instance, a patch with no aloe vera should have been compared with a second patch identical (i.e with the same concentration of active ingredient) except for the fact of containing aloe vera. However, in the experiment of example 1 the patches having a different concentration of aloe vera also have a different concentration of buprenorphine. This does not allow an assessment of the effects due to aloe vera alone.

- 3.2.7 Thus, example 1 of the patent does not support the respondent's conclusion that the inclusion of aloe vera in a matrix patch results in an increase of the transdermal absorption of the active ingredient.
- 3.2.8 As a further argument, the respondent suggested that the copolymers constituting the adhesives provide the advantage of preventing the crystallisation of the

active ingredient inside the patch. This effect was shown in an experimental report submitted during the examination phase.

- 3.2.9 In this regard the Board observes that the patent application does not provide any information as to this technical effect promoted by the use of SBS or SB copolymers as constituents of the adhesive. More generally, the problem of avoiding the crystallisation of the active ingredient is nowhere mentioned in the original application.

The description underlines the fact that only a limited number of drugs are bioavailable via transdermal application because of the skin's drug penetration resistance (paragraph [0003]). This problem is solved by the use of aloe vera as drug penetration enhancer (page 2, lines 54 to 57). However, the description does not establish any relationship between the problem of increasing the transdermal absorption and the effect subsequently invoked by the respondent which is associated with the composition of the adhesive. In this context, it is also noted that during the first instance proceedings the respondent presented the effect of the adhesive on the prevention of the crystallisation of the active ingredient as an aspect concerning the storage stability of the product (letter of 24 February 2014, page 11).

- 3.2.10 According to the established case law of the boards of appeal an alleged effect of a technical feature cannot be taken into account when determining the technical problem if this effect cannot be deduced by the skilled person from the application as filed (Case Law of the Boards of Appeal of the EPO, 8th edition 2016, I.D. 4.4.2). In the Board's view, this is the case for the

effect claimed by the respondent with regard to the prevention of the crystallisation of the active ingredient. It follows that this effect cannot be considered for the formulation of the technical problem.

3.2.11 The technical problem underlying the invention is therefore defined as the provision of an alternative transdermal patch for opioid analgesic drugs.

3.3 Obviousness

3.3.1 Document D9 describes as a preferred embodiment patches containing plant extracts such as aloe vera extracts (see paragraph linking columns 4 and 5). Thus, on the basis of this information, the skilled person would consider obvious to include aloe vera in the composition of a patch. Furthermore, document D16 teaches that aloe vera, when combined with other substances, has the ability to help these substances to penetrate more easily and deeply into the skin (see section "Penetrating burn remedy"). According to the description of the patent, the diffusion of a substance through the stratum corneum and the epidermis are mechanisms involved in the transdermal absorption of the substance (see paragraph [0004]). Hence, document D16 would provide an additional motivation to include aloe vera in a transdermal patch.

3.3.2 As to the composition of the adhesive, D9 refers to copolymers containing styrene and butadiene as monomers (column 3, lines 12 and 13). However, it does not mention specifically the SB and SBS copolymers.

The use of these products as components of adhesives is in any case known from the state of the art as

acknowledged in paragraph [0064] of the description of the patent-in-suit. For instance, D7 describes an adhesive matrix containing a SBS block copolymer. Hence, the choice of SB or SBS copolymers as components of the adhesive composition does not involve any inventive activity.

- 3.4 It follows from the above that claim 1 of the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary requests

4. Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. Hence, this request fails to comply with Article 56 EPC either.
5. The modifications introduced in claim 1 of auxiliary requests 2 to 5 concern the limitation of the opioid analgesic to buprenorphine and the indication that the adhesive consists of a SBS or SB copolymer (i.e. deletion of the option "comprising", see point IV above).
- 5.1 Document D9 explicitly mentions buprenorphine as a suitable active ingredient. Hence, the restriction concerning the active ingredient does not provide any inventive contribution to the subject-matter of the claims.
- 5.2 The amendment concerning the composition of the adhesive was apparently introduced by the respondent in response to objections put forward by the appellant under Article 100(b) and 100(c) EPC. This amendment has no impact on the assessment of inventive step. Nor has the respondent submitted any argument in this respect.

5.3 In the light of the above that Board concludes that auxiliary requests 2 to 5 do not fulfil the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated